REMARKS

Following entry of the above amendment, claims 1-37 will be pending in the application, with claims 1-5 and new claims 35-37 presently under examination. The above amendments to claims 1, 4 and 5 are supported in the specification, e.g., at page 5, lines 28-30. The subject matter of original claim 3 is now divided between amended claim 3 and new claim 35. Support for new claims 36 and 37 can be found throughout the specification. No new matter has been added.

The claims cover substantially pure polypeptides comprising an amino acid sequence at least 85% identical to SEQ ID NO:1 or 2, SEQ ID NO:2 being a subset of SEQ ID NO:1. Each of the claimed polypeptides contains at least one PDZ domain sequence that interacts with a protein having a hydrophobic amino acid region at its C-terminus.

All of the claims under examination were rejected on a number of grounds, discussed in detail below.

I. Rejections under 35 U.S.C. §101

Claims l-5 were rejected under 35 U.S.C. § 101 as lacking patentable utility. The Examiner asserts that the claimed invention is not supported by a specific and substantial asserted utility or a well established utility. More specifically, the Examiner refers to the presently claimed polypeptides as "orphan proteins" that "have not been shown to be involved in the binding of specific proteins, have not been shown to be a disease marker, have enzymatic activities or be involved in a physiological process that one would want to manipulate for clinical effect..." According to the Office Action at page 3, "The numerous uses of the claimed invention (pages 19-26), are not specific, substantial or credible utilities because Applicants have failed to disclose which other proteins the instant proteins interacts with." Applicants traverse this rejection, particularly as it may be applied to the claims as presently amended.

The USPTO issued Utility Guidelines Training Materials to instruct Examiners on how to interpret and apply the utility requirement in certain fact situations. Example 12 of these Training Materials, entitled "Receptors", is particularly analogous to the present situation.

Example 12 describes an hypothetical specification that discloses a novel protein, A, isolated from a cell membrane preparation. A is the binding partner for protein X, a protein with no identified function. Based solely on these facts, the hypothetical applicant characterizes isolated protein A as a receptor for protein X and later claims "isolated receptor A". The specification further discloses (1) a binding assay for determining other materials that will bind to the receptor and thus effect therapeutic control over the receptor, and (2) a method of making monoclonal antibodies that bind to the receptor. Performing the requisite utility analysis, Example 12 reasons that a method of identifying materials that bind to a specific receptor and a method of making monoclonal antibodies that bind to a specific receptor both qualify as "specific" utilities, thus meeting that aspect of the utility guidelines' criteria. Example 12 goes on to state that neither of the two asserted utilities is, under the facts of that hypothetical case, "substantial." The basis for this conclusion lies in the fact that

> the only utility asserted for the identified materials is a therapeutic to effect control over receptor A. Since neither the specification nor the art of record disclose any diseases or conditions associated with receptor A, a method of treating an unspecified, undisclosed disease or condition, does not define a "real world" context of use.

Thus, if the Example 12 specification had disclosed a specific disease or condition that could potentially be treated with either (1) materials identified in the screening assay as binding to receptor A, or (2) monoclonal antibodies specific for receptor A, then the requisite "real world" context of use would have been present and the "substantial" criterion met.

Following the analogy to Example 12, Applicants submit that the presently claimed invention clearly meets both the "specific" and "substantial" utility criteria as currently applied by the Office. (The "credible" criterion, not addressed in Example 12, will be discussed below.) Just as in Example 12, Applicants have asserted that the presently claimed polypeptides can be used in screening methods to identify materials that bind to the polypeptides specifically, or in methods of making monoclonal antibodies that bind to the polypeptides specifically. In the absence of any rationale as to why these utilities could be "specific" in the Training Materials context and not in the present context, Applicants submit that they indeed meet this criterion and request that the Examiner acknowledge same.

With respect to the second criterion, Applicants note that the underlying reason supporting the conclusion of "no substantial utility" in Example 12 is the fact that no function was associated with protein X in that hypothetical specification. In contrast, the protein(s) that bind to the PDZ-domain containing polypeptides of the instant invention (i.e., proteins having the hydrophobic amino acid region at their C-terminus) do have identified functions. As noted in the specification, "most of these proteins are transmembrane proteins and are presumed to function in signal transduction." See specification at page 2, lines 26-30. See also (1996) *TIBS* 21:455-458, and Yanagisawa et al. (1997) *J. Biol. Chem.*, 272:7167-7172. As such proteins are involved in "neural transmission, apoptosis, and malignant conversion, they have recently drawn attention as targets for developing pharmaceuticals." (Carryover sentence of pages 2-3 in specification) Thus, materials identified in the described "drug screen" do have a "real world" utility that meets the "substantial" criterion as that criterion is interpreted in the Training Materials. Likewise, antibodies that bind the presently claimed polypeptides undeniably possess "real world" utilities in that they can be used as a reagent in the drug screening assays, or as a means to immunoprecipitate complexes between the presently claimed polypeptides and the proteins to which they bind, or as potential therapeutics themselves. Given the connection between PDZ domain-binding proteins and disease, Applicants maintain that the presently claimed polypeptides possess asserted utilities that are both specific and substantial.

The Utility Guidelines issued by the Office require that the asserted utility be not only specific and substantial, but also "credible." According to the Training Materials,

> An assertion is credible unless (A) the logic underlying the assertion is seriously flawed, or (B) the facts upon which the assertion is based are inconsistent with the logic underlying the assertion.

The Examiner has not suggested either that the logic underlying Applicants' asserted utilities is seriously flawed, nor that the facts upon which the assertions are based are inconsistent with the logic underlying those assertions. Accordingly, Applicants submit that the utilities asserted for the present invention meet the credibility prong of the utility requirement as currently interpreted by the Office. As all three prongs of the test are met, the utilities asserted in the specification satisfy the utility requirement, and the rejection should be withdrawn.

Moreover, the PDZ-domain containing polypeptides of the present invention have at least two additional, well-established utilities (e.g., a utility that is well known, immediately apparent and/or implied by the specification, taken in context the knowledge of the prior art). First, the claimed polypeptides can be used to detect and/or measure in a biological sample the presence of PDZ-binding transmembrane proteins, proteins that in turn have a known correlation with the disease conditions noted above. Second, since the presently claimed polypeptides were first identified by differential expression in TNFα-induced human vascular endothelial cells (see, e.g., Example 1 of the specification at pages 32-33), antibodies specific for the claimed polypeptides are presumptively useful for discriminating between vascular endothelial cells induced by TNFα (a cytokine with well-known biological significance) and those not induced. This particular "well-established utility" is comparable to the "well-established utility" that is discussed near the end of the Training Materials' Example 12, and that is said to be adequate to meet the utility requirement.

Thus, the claimed polypeptides more than meet the utility requirements of § 101, possessing both asserted and well-established utilities that are specific, substantial, and credible. Withdrawal of the rejection under §101 is therefore respectfully requested.

II. Rejection under 35 U.S.C. § 112, first paragraph

Claims 1-5 were rejected under 35 U.S.C. § 112, first paragraph, as failing to adequately teach how to use the invention for the reasons give above with respect to utility. According to the Examiner, since the claimed invention is not supported by a specific, substantial and/or well established utility for the reasons set forth above, one skilled in the art would not know how to make, and use the claimed invention so that it would operate as intended without undue experimentation (e.g., lack of enablement based on lack of utility).

This ground for rejection is overcome by the arguments set forth above with respect to utility.

Claims 1-5 were further rejected under 35 U.S.C. § 112, first paragraph, for lacking enablement. In particular, the Examiner asserts that the claimed invention, while being enabling for proteins of SEQ ID NOs:1 and 2, does not provide enablement for:

- proteins at least 85% or 90% identical to SEQ ID NOs:1 and 2;

- proteins of SEQ ID NOs:1 and 2 with up to 50 conservative substitutions; and

- proteins encoded by nucleic acids that hybridize under high stringency conditions to probes of SEQ ID NOs:3, 59, 75, 78, 79, 80, or 81.

Applicants remind the Examiner that a specification is presumed to be in compliance with the enablement requirement of § 112, first paragraph. The burden is on the Office to establish a reasonable basis to question enablement. The test of enablement is whether one reasonably skilled in the art could make and use the claimed invention (here, proteins) from the disclosures in the patent coupled with information known in the art, without undue experimentation. For an Examiner to sustain a rejection of the claims in this case on the grounds of enablement, she would have to provide evidence that the claimed proteins could not be made or used, for any purpose, without undue experimentation. No such evidence has been presented. See MPEP 2164, particularly 2164.01 and 2164.05. Moreover, to expedite prosecution, Applicants have restricted the claimed polypeptides to those that retain the critical function of binding to proteins having a hydrophobic amino acid region at their C-terminus.

The claims as amended encompass both the wild-type proteins (e.g., SEQ ID NOs:1 and 2) and "functional derivatives" thereof. A functional derivative is defined as a protein that has an amino acid sequence that differs (to some degree) from that of the wild-type protein yet "maintains the affinity to the other proteins characteristic of the PDZ domain" (See p. 9, lines 13-14). This affinity normally arises from the affinity to a hydrophobic amino acid region that exists in the C-terminal ends of the other proteins. (p. 9, lines 14-16).

The instant specification provides ample guidance as to how to make and use such functional derivatives as claimed. For example, the instant specification describes the exact locations of the nine and eight PDZ domains within SEQ ID NOs:1 and 2, respectively (See p. 6, lines 12-19 and lines 28-32, respectively). Accordingly, to maintain the requisite affinity, it is preferable that any modifications or alterations should occur outside the PDZ sequences themselves. Exemplary alteration methods are set forth at p. 10, line 3 - p. 11, line 12.

Moreover, guidance with regards to conservative amino acid substitutions is set forth at p. 11, line 21 - p. 12, line 2. Finally, instruction with regards to identifying proteins within a particular range of identity (e.g., at least 85%) is set forth on p. 12, line 18 top. 13, line 2. Thus, Applicants submit that one of ordinary skill in the art could readily make and use the claimed invention (herein wild-type proteins and non-wild-type proteins that meet the criteria of the claims) from the disclosures in the patent, coupled with information known in the art, without undue experimentation. Certainly the Examiner will agree that making proteins throughout the scope of the instant claims is well within the abilities of molecular biologists of ordinary skill. Thus making the claimed polypeptides is not an issue. Further, since all of such proteins will have at least one PDZ domain (that being a limitation of the claim), they can be expected to bind to a protein that has a hydrophobic amino acid region at its C-terminus. Their use will be apparent to those of ordinary skill. Applicants therefore are unsure of the source of the Examiner's concerns regarding claim scope.

In light of the above, Applicants submit that the instant specification is enabling not only for the wild type proteins of SEQ ID NOs:1 and 2, but also for proteins at least 85% or 90% identical to SEQ ID NOs:1 and 2; proteins of SEQ ID NOs:1 and 2 with up to 50 conservative substitutions; and proteins encoded by nucleic acids that hybridize under high stringency conditions to probes of SEQ ID NOs:3, 59, 75, 78, 79, 80, or 81. Withdrawal of the rejection is therefore respectfully requested.

III. Rejections under § 112, second paragraph

Claims 1 and 2 were rejected under 35 U.S.C. § 112, second paragraph, for failing to particularly point out and distinctly claim that which Applicants regard as the invention. The Examiner objects to the term "PDZ domain sequence" in claim 1, saying that it is vague and indefinite.

Applicants respectfully traverse this rejection. Not only is the term "PDZ domain sequence" an art-recognized term (see Background, p. 1, lines 15-29), but it is also amply defined and described in the instant specification. Specifically, the term "PDZ domain sequence" refers to a sequence having 80 to 90 amino acids containing a four amino acid motif that consists of "Gly-Leu-Gly-Phe" (GLGF) or similar amino acids (see p. 5, lines 21-25). The

PDZ domain sequence can be repeated a number of times (one to thirteen) and is also called the GLGF repeat or the DHR domain (See Background, p. 1-2). Accordingly, the metes and bounds of the term "PDZ -domain sequence" would be well understood by one skilled in the art, when read in light of the specification and in the context of the prior art. Withdrawal of the rejection is therefore requested.

Attached is a marked-up version of the changes being made by the current amendment.

Applicant asks that all claims be allowed. Enclosed is a $138 check for excess claim fees and a $920 check for the Petition for Extension of Time fee. Please apply any other charges or credits to Deposit Account No. 06-1050.

Respectfully submitted,

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Version with markings to show changes made

In the claims:

Claims 1, 3, 4 and 5 have been amended as follows:

1. (Amended) A substantially pure polypeptide comprising an amino acid sequence at least 85% identical to SEQ ID NO:1 or 2, wherein the polypeptide contains [a] at least one PDZ domain sequence, wherein at least one of said PDZ domain sequences interacts with a protein that has a hydrophobic amino acid region at its C-terminus.

3. (Amended) A substantially pure polypeptide comprising SEQ ID NO:1 [or 2].

4. (Amended) A substantially pure polypeptide comprising the amino acid sequence of SEQ ID NO:1 or 2, with up to 50 conservative amino acid substitutions, wherein the polypeptide contains [a] at least one PDZ domain sequence, wherein at least one of said PDZ domain sequences interacts with a protein that has a hydrophobic amino acid region at its C-terminus.

5. (Amended) A substantially pure polypeptide encoded by a nucleic acid that hybridizes under high stringency conditions to a probe the sequence of which consists of SEQ ID NO:3, 59, 75, 78, 79, 80, or 81, wherein the polypeptide contains [a] at least one PDZ domain sequence, wherein at least one of said PDZ domain sequences interacts with a protein that has a hydrophobic amino acid region at its C-terminus.